REMARKS

Applicants have amended the specification and claims to comply with 37 C.F.R. §§ 1.821-1.825 for nucleotide and amino acid sequences disclosed. Applicants have amended claims 4, 22, and 27, part (a) by replacing "Gln" with "Glu" and part (e) by replacing "thr" with "Thr" to correct typographical errors in the original claims. Support for the correction to part (a) of claims 4, 22, and 27 is provided throughout the specification, such as in originally filed Figure 1A, for example, in which the nucleic acid sequence corresponding to the peptide of part (a) contains the Glu codon, GAG, at amino acid 10 in Figure 1A. Support for capitalization of Thr in part (e) of claims 4, 22, and 27 is also found in originally filed Figure 1A at amino acid 156. No new matter is introduced by these amendments and their entry is respectfully requested.

Accordingly, in view of the remarks, Applicants submit that this application is in condition for allowance. Early notice to this effect is solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

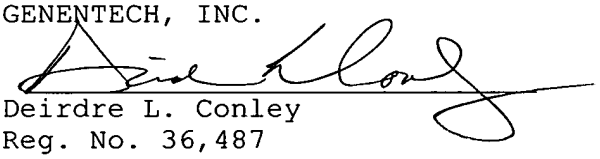
If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at the telephone number below.

This Preliminary Amendment is submitted with a transmittal letter, Sequence Listing, Diskette and Certificate Re: Sequence Listing, and Copy of Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures in compliance with 37 C.F.R. §§ 1.821-1.825 without fees because Applicants believe that the documents are timely filed and fees are not necessary. In the unlikely event that this Preliminary Amendment is separated from the transmittal letter, or other documents or if fees or credits are due, Applicants hereby authorize the Commissioner to deducted fees or make credits to our Deposit Account No. 07-0630 and hereby petition the Commissioner for any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,

GENENTECH, INC.

Date: August 29, 2001

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Amendments to the specification and claims are indicated as follows: Strike through in brackets denotes deleted text. Underline and bold denotes added text.

Paragraph beginning at line 34 of page 4 has been amended as follows:

Figure 1 shows the cDNA **(SEQ ID NO:1)** and predicted amino acid sequence **(SEQ ID NO:2)** of the rat ovarian LH/CG-R. In the figure, chemically determined peptide sequences are indicated by bars atop corresponding sequences, with residues differing from those predicted indicated by white bars. Amino acid numbering begins at the N-terminal sequence found for the mature intact receptor **(SEQ ID NO:3)**, with negative numbers for the encoded signal sequence. Putative extracellular N-linked glycosylation sites are marked by inverted triangles, and the proposed membrane-spanning hydrophobic sequences are enclosed in boxes. Overlined residues show location of similarity to soybean lectin (L.O. Vodkin et al., Cell 34:1023 (1983); D.J. Schnell et al., J. Biol. Chem. 262:7220 (1987) (Diflorus)).

Paragraph beginning at line 35 of page 5 has been amended as follows:

Figure 6a and 6b show the cDNA **(SEQ ID NO:5)** and predicted amino acid sequence **(SEQ ID NO:6)** of rat testicular FSH-R. Amino acid numbering begins at the N-terminal sequence for the predicted mature receptor protein **(SEQ ID NO:7)**, with negative numbers denoting the signal sequence.

Paragraph beginning at line 32 of page 42 has been amended as follows:

TABLE 2

ks: AAGGAGCTG(AG)TGGC(AG)C(C)GGAAGCCTGAGCCCAATGACTTC
(TC) (TC) (A)
GCCCCTGATGGTGCCCT **(SEQ ID NO:9)**

rsrc: TGCACCTCCTCGAAGCAGTTGCCATACAGCTTCAGGGTCACA(CT)CTC **(SEQ ID NO:10)**
(GA)

fsrc: ACG(GG)GTCCAGGATG(CT)TGTGGCACCCTGGAAGGC(T)CC **(SEQ ID NO:11)**
(AT) (GA) (C)

Paragraph beginning at line 23 of page 43 has been amended as follows:

The nucleotide **(SEQ ID NO:1)** and predicted amino acid sequence **(SEQ ID NO:2)** of the rat LH/CG-R cDNA with 43 nucleotides of 5' flanking and 759 nucleotides of 3' flanking sequence are shown in Figure 1. The translation initiation codon at position 1 defines the start of a 2100 nucleotide long open reading frame which encodes all independently determined peptide sequences. The predicted N-terminal amino acid sequence constitutes a signal peptide of 26 residues (G. von Heijne, Nucleic Acids Res. 14:4683 (1986)). The sequence following the signal peptide corresponds to the peptide determined from the uncleaved LH/CG-R (SEQ ID NO:3) polypeptide. Hence, the mature LH/CG-R was concluded to begin with Arg and to be composed of 674 amino acid residues (Mr ≈ 75 kDa).

Paragraph beginning at line 23 of page 44 has been amended as follows:

From these data, we postulate that the LH/CG receptor consists of a large N-terminal extracellular domain **(SEQ ID NO:4)** attached to a region that traverses the plasma membrane seven times, terminating with a small C-terminal cytoplasmic tail.

Paragraph beginning at line 26 of page 44 has been amended as follows:

It is likely that the extracellular domain **(SEQ ID NO:4)** is involved in binding the large glycoprotein hormones CG and LH. This assignment is consistent with biochemical data showing that a 64kDa water-soluble fragment of the LH/CG receptor can bind CG (Keinanen, K.P., Biochem. J. 239:83 (1986)) and with data from collagenase-treated cells.

Paragraph beginning at line 30 of page 44 has been amended as follows:

The extracellular region **(SEQ ID NO:4)** of the receptor has many notable features. Firstly, there are six potential sites for N-terminal glycosylation. Preliminary data suggests that most of these sites are likely to be glycosylated. Secondly, there is a site consisting of 10 amino acids which is identical to a region in the soybean lectin (Schnell, K.J. et al., J. Biol. Chem. 262:7220 (1987)). It is well known that although the deglycosylated forms of CG and LH bind to the LH/CG receptor, they elicit little or no biological activity. Therefore, it will be interesting to test whether this site on the LH/CG receptor is involved in recognition of the carbohydrate chains of the hormone.

Paragraph beginning at line 37 of page 44 has been amended as follows:

Thirdly, the extracellular domain **(SEQ ID NO:4)** can be aligned into a 14-fold imperfectly repeated motif of approximately 25 amino acids. The composition of this leucine-rich motif is common to a number of other proteins. These include proteins of such widely diverse (or unknown) functions as the yeast adenylate cyclase (Kataoka, T. et al., Cell 43:493-505 (1985)), the Toll developmental gene of Drosophila (Hashimoto, C. et al., Cell 52:269 (1988)), the human serum alpha2 glycoprotein (Takahashi, N. et al., Proc. Natl. Acad. Sci. (U.S.A.) 83:1906 (1985)), the platelet 1b receptor for von Willebrand factor and thrombin (Lopez, J.A. et al., Proc. Natl. Acad. Sci. (U.S.A.) 84:5615 (1987)), and the extracellular matrix proteoglycan PG40 (Krusius, T. et al., Proc. Natl. Acad. Sci. (U.S.A.) 83:7683 (1986)). It should be pointed out that of these proteins, only PG40 appears to share an overall amino acid homology with the extracellular region of the LH/CG receptor. The biological significance of this leucine-rich repeat structure is not really known. It has been suggested that it may be able to form an amphipathic helical

structure and, therefore, may be involved in interacting with both an aqueous environment and the plasma membrane. This suggests that upon binding CG or LH the extracellular domain of the LH/CG receptor may interact with the membrane-spanning regions of the receptor.

Paragraph beginning at line 24 of page 48 has been amended as follows:

The N-terminal half of the polypeptide chain (residues 1-341) (SEQ ID NO:4) presumably constitutes the extracellular domain (Fig. 1). Consonant with the glycoprotein nature of the LH/CG-R, there are six potential N-linked glycosylation sites within this domain. Preliminary evidence suggests that most of these sites are indeed glycosylated and this may account for the difference in molecular weight between the natural LH/CG-R (Mr ≈ 93 kDa) and the predicted mature unglycosylated polypeptide (Mr ≈ 75 kDa). In fact, molecular weights of CNBr fragments estimated by gel electrophoresis are consistent with an average contribution of 5-6 kDa per glycosylation site by oligosaccharide side chains.

Paragraph beginning at line 35 of page 53 has been amended as follows:

Polyadenylated RNA isolated from rat testicular Sertoli cells was used as a template for reverse transcriptase. The resulting cDNA served for the construction of a library in lgt10. An aliquot (1x106 clones) was screened for clones with sequence similarity to two probes derived from the LH/CG-R cDNA (nucleotides 1-483 and 1499-2604). Several positive clones were isolated and cloned cDNAs sequenced as described in F. Sanger et al., Proc. Natl. Acad. Sci. USA, 74:5463-5467 (1977) after subcloning into M13 vectors (J. Vieira and J. Messing, Meth Enzymol., 153:3-11 (1987)). The nucleotide **(SEQ ID NO:5)** and predicted amino acid **(SEQ ID NO:6)** sequences of this receptor are shown in Figure 6.

Paragraph beginning at line 4 at page 54 has been amended as follows:

The translation initiation codon at position 1 defines the start of a 2076 nucleotide open reading frame specifying an N-terminal 17 residue signal sequence followed by a largely hydrophilic domain of 348 residues of putatively extracellular location **(SEQ ID NO:8)**. This domain contains

three N-linked glycosylation sites. It is followed by a structure of 264 residues which comprises seven transmembrane segments. These segments are the hallmark of G protein-coupled receptors. Similar to other such receptors, the 63 residue C-terminus of the FSH-R is proposed to be located intracellularly and contains several amino acids (Ser, Thr, Tyr) whose phosphorylation may regulate receptor activity (K. Palczewski et al., Biochemistry, 27:2306-2313 (1988); J.L. Benovic et al., Proc. Natl. Acad. Sci. USA, 83:2797-2801 (1986)). However, these residues are not part of consensus phosphorylation sites as in other receptors. The mature FSH-R **(SEQ ID NO:7)** is predicted to comprise 675 amino acids (75K mol. wt.) and to constitute an integral membrane glycoprotein.

In the Claims:

Claims 4, 22, and 27 have been amended as follows:

4. (Amended) The pharmaceutical composition of claim 2 wherein said LH/CG hormone receptor molecule contains at least one sequence selected from the group consisting of:

(a) Glu-Leu-Ser-Gly-Ser-Arg-Cys-Pro-[~~Gln~~] **Glu** -Pro **(SEQ ID NO:12)**;

(b) Pro-Arg-Ala-Gly-Leu-Ala-Arg-Leu-Ser-Leu **(SEQ ID NO:13)**;

(c) Leu-Asn-Glu-Val-Val-Lys-Ile-Glu-Ile-Ser **(SEQ ID NO:14)**;

(d) Ser-Glu-Leu-Leu-Ile-Gln-Asn-Thr-Lys-Asn **(SEQ ID NO:15)**;

(e) Met-Asn-Asn-Glu-Ser-Val-[~~thr~~] **Thr** -Leu-Lys-Leu **(SEQ ID NO:16)**;

(f) Thr-Leu-Thr-Tyr-Pro-Ser-His-Cys-Cys-Ala **(SEQ ID NO:17)**;

(g) Val-Leu-Ile-Trp-Leu-Ile-Asn-Ile-Leu-Ala **(SEQ ID NO:18)**;

(h) Val-Phe-Ala-Ser-Glu-Leu-Ser-Val-Tyr-Thr **(SEQ ID NO:19)**;

(i) Ala-Ile-Leu-Ile-Phe-Thr-Asp-Phe-Thr-Cys **(SEQ ID NO:20)**;

(j) Phe-Thr-Lys-Ala-Phe-Gln-Arg-Asp-Phe-Leu **(SEQ ID NO:21)**; and

(k) Arg-Ala-Glu-Leu-Tyr-Arg-Arg-Lys-Glu-Phe **(SEQ ID NO:22)**.

22. (Amended) The recombinant molecule of claim 21 wherein said LH/CG hormone receptor molecule contains at least one sequence selected from the group consisting of:

(a) Glu-Leu-Ser-Gly-Ser-Arg-Cys-Pro-[~~Gln~~] **Glu** -Pro **(SEQ ID NO:12)**;

(b) Pro-Arg-Ala-Gly-Leu-Ala-Arg-Leu-Ser-Leu **(SEQ ID NO:13)**;

(c) Leu-Asn-Glu-Val-Val-Lys-Ile-Glu-Ile-Ser **(SEQ ID NO:14)**;

(d) Ser-Glu-Leu-Leu-Ile-Gln-Asn-Thr-Lys-Asn **(SEQ ID NO:15)**;

(e) Met-Asn-Asn-Glu-Ser-Val-[~~thr~~] **Thr** -Leu-Lys-Leu **(SEQ ID NO:16)**;

(f) Thr-Leu-Thr-Tyr-Pro-Ser-His-Cys-Cys-Ala **(SEQ ID NO:17)**;

(g) Val-Leu-Ile-Trp-Leu-Ile-Asn-Ile-Leu-Ala **(SEQ ID NO:18)**;

(h) Val-Phe-Ala-Ser-Glu-Leu-Ser-Val-Tyr-Thr **(SEQ ID NO:19)**;

(i) Ala-Ile-Leu-Ile-Phe-Thr-Asp-Phe-Thr-Cys **(SEQ ID NO:20)**;

(j) Phe-Thr-Lys-Ala-Phe-Gln-Arg-Asp-Phe-Leu **(SEQ ID NO:21)**; and

(k) Arg-Ala-Glu-Leu-Tyr-Arg-Arg-Lys-Glu-Phe **(SEQ ID NO:22)**.

27. (Amended) The recombinant molecule of claim 9 wherein said molecule contains at least 10 nucleotides selected from the group consisting of:

(a) Glu-Leu-Ser-Gly-Ser-Arg-Cys-Pro-[~~Gln~~] **Glu** -Pro **(SEQ ID NO:12)**;

(b) Pro-Arg-Ala-Gly-Leu-Ala-Arg-Leu-Ser-Leu **(SEQ ID NO:13)**;

(c) Leu-Asn-Glu-Val-Val-Lys-Ile-Glu-Ile-Ser **(SEQ ID NO:14)**;

(d) Ser-Glu-Leu-Leu-Ile-Gln-Asn-Thr-Lys-Asn **(SEQ ID NO:15)**;

(e) Met-Asn-Asn-Glu-Ser-Val-[~~thr~~] **Thr** -Leu-Lys-Leu **(SEQ ID NO:16)**;

(f) Thr-Leu-Thr-Tyr-Pro-Ser-His-Cys-Cys-Ala **(SEQ ID NO:17)**;

(g) Val-Leu-Ile-Trp-Leu-Ile-Asn-Ile-Leu-Ala **(SEQ ID NO:18)**;

(h) Val-Phe-Ala-Ser-Glu-Leu-Ser-Val-Tyr-Thr **(SEQ ID NO:19)**;

(i) Ala-Ile-Leu-Ile-Phe-Thr-Asp-Phe-Thr-Cys **(SEQ ID NO:20)**;

(j) Phe-Thr-Lys-Ala-Phe-Gln-Arg-Asp-Phe-Leu **(SEQ ID NO:21)**; and

(k) Arg-Ala-Glu-Leu-Tyr-Arg-Arg-Lys-Glu-Phe **(SEQ ID NO:22)**.